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(54) Title: SUSTAINED RELEASE MATRIX COMPOSITION

(57) Abstract

Sustained release microparticule compositions including a core element comprising an active ingredient of very low solubility and at least two polymers. The core element is optionally coated with an enteric coating and includes dihydropyridines, especially nifedipine as the active ingredient. The compositions are prepared by spraying a core seed with the core element formulation in a fluidised bed coater, centrifugal granulator or spheronizer and drying the composition. The compositions are useful for treating cardiovascular related conditions.

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SUSTAINED RELEASE MATRIX COMPOSITION

The present invention relates to sustained release pharmaceutical microparticle compositions in particular sustained release pharmaceutical microparticle compositions including an active ingredient of very low solubility in water, and to a method of preparing same.

As is known in the prior art it is desirable in the treatment of a number of diseases both therapeutically and prophylactically to provide the active pharmaceutical ingredient in a sustained release form. This is particularly desirable for the treatment of diseases which have to be treated for prolonged periods such as, for example, hypertension. In these instances it is desirable to minimize the frequency of intake of medicaments. This is not only more pleasant for the patient it also increases the reliability of treatment by diminishing the disadvantages of irregular intakes and results in a more nearly constant therapeutic level of active ingredient in the body. Further this minimizes the risks of the active blood levels not being within the required therapeutic indices and avoids blood level peaks usually found after intake of rapid release forms.

Whilst there is known in the prior art numerous sustained release formulations the extension of such sustained release regimen to active pharmaceutical ingredients of very low solubility in water has been extremely limited.

For example, active ingredients of very low solubility include the dihydropyridine compounds which are used as cardiovascular agents. Difficulties often occur in the pharmaceutical formulation of these potent active compounds due to their very low solubility, which can result in erratic and/or poor absorption of the drug from pharmaceutical dosage forms.

One such technique of enhancing drug absorption is to formulate a solid dispersion or co-precipitate system. This technique is well known and is extensively discussed in the article "Pharmaceutical Applications of Solid Dispersion Systems" by Win Loung Chiou and Sidney

Riegelman. J. of Pharm. Sci. Vol. 60, No. 9, September 1971 (1281-1301) which is incorporated herein by reference.

The term Solid Dispersion or Co-Precipitate refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method and is hereinafter simply referred to as a "matrix". Solid dispersions may also be called solid-state dispersions. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this definition.

Whilst numerous attempts have been made to prepare sustained release forms of pharmaceutical formulations including dihydropyridine compounds as the active ingredient, it has not been possible to date to formulate a matrix composition in microparticle form which in use will release such active ingredients at a sufficient rate to provide a therapeutic level of active for extended periods of time, preferably for at least approximately 12 hours or more, preferably 24 hours or more.

Accordingly it is an object of the present invention to overcome, or at least alleviate, one or more of the difficulties related to the prior art.

Accordingly in a first aspect of the present invention there is provided a sustained release matrix pharmaceutical microparticle composition including

a core element including

an active ingredient of very low solubility; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

By the term "matrix" as used herein we mean that the active ingredient is in a solid dispersion or co-precipiate with a polymer.

By the term "microparticle composition" as used herein we mean pellets or granules. Preferably the microparticle composition is in the form of pellets.

By "sustained release" as used herein we mean at

least a two fold reduction in dosing frequency as compared to drug presented as a conventional dosage form (e.g. as a solution or a prompt drug-releasing, conventional dosage form). [U.S. Pharmacopeia [USPXXI](1985)(xivi)]. e.g. for at least approximately 12 hours or greater, preferably for at least approximately 24 hours.

By "active ingredient of very low solubility" as used herein we mean pharmaceutically active, orally acceptable ingredients having an aqueous solubility of approximately 1 in 10^3 parts of solvent per part of solute or less, preferably at least approximately 1 in 10^4 parts of solvent per part of solute or less.

By "bioavailability" as used herein we mean the extent to which the active drug ingredient is absorbed from the microparticle composition and which reaches the general circulation intact.

The active ingredient of very low solubility may be selected from the group consisting of dihydropyridines for example Nifedipine, Nitrendipine, Nisoldipine, Nimodipine, Nicardipine, Darodipine, Isradipine, Niludipine, Amlodipine, Felodipine, Lacidipine, BBR-2160, Cronidipine, Diperdine, Mepirodipine, Nilvadipine, Oxodipine, Sangandipine, Clinidipine, Manidipine, Benidipine, pharmaceutically acceptable isomers and salts thereof and mixtures thereof. The active ingredient in the final composition is preferably in crystalline form.

The active ingredient may be present in the core element in any suitable effective amount. The amount of active ingredient is dependent on the potency of the active ingredient and on the desired dosage strength and volume of a unit dose of the drug product. The active ingredient may be present in amounts of approximately 0.1 to 99%, preferably 1 to 95% by weight, based on the total weight of the core element. The active ingredient may preferably be a dihydropyridine compound, more preferably nifedipine. The compound nifedipine may be present in amounts of approximately 5 to 70% by weight, preferably 15 to 50% by weight, based on the total weight of the core element.

In the following description the active ingredient

of very low solubility will be illustrated by reference to the dihydropyridine, nifedipine. However this is illustrative only and the invention is in no way restricted thereto. Nifedipine is a cardiovascular drug and is a potent relaxant of arterial smooth muscle. It dilates both the main coronary arteries and arterials both in normal and in ischaemic myocardioregions. Nifedipine is also a potent inhibitor of coronary artery spasm. Nifedipine is thus indicated in the long-term management of angina pectoris due to coronary heart disease. The usual dose is one 10 mg capsule three times daily but up to two capsules four times daily may be taken. The benefits of a sustained release microparticle composition including nifedipine are thus obvious.

The polymeric component of the sustained release matrix pharmaceutical composition may include, in addition to the active ingredient,

a polymer which is at least partially water-soluble (water-soluble polymer); and

a polymer which is substantially insoluble at acidic pH but at least partially soluble at a less acidic to basic pH (enteric polymer).

The water-soluble polymer may be selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof. Polyethylene glycols or Macrogols of intermediate molecular weights (4000-12000) have been found to be suitable. The polyethylene glycol sold under the trade designation PEG 6000 has been found to be suitable.

The water-soluble polymer may be present in the core element in amounts of from approximately 10 to 80%, preferably 15 to 60% by weight, based on the total weight of the core element.

The enteric polymer, when present, may be selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methyl- cellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac,

cellulose acetate trimellitate and mixtures thereof. Particularly preferred enteric polymers include synthetic or semi-synthetic resins bearing carboxyl groups. The hydroxypropyl methylcellulose phthalates sold under the trade designations HP50 or HP55 have been found to be suitable.

The enteric polymer may be present in the core element in an amount of from 0 to approximately 50% by weight, preferably 0.1 to 20% by weight, more preferably 0.5 to 10% by weight, based on the total weight of the core element.

Accordingly, in a preferred aspect of the invention there is provided a sustained release pharmaceutical microparticle composition including

a core element including

approximately 1 to approximately 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight of a polymeric component in a matrix therewith including

a water-soluble polymer; and

an enteric polymer;

and optionally

an enteric coating over the core element.

The core element may further include other compounding ingredients including plasticisers and fillers. Accordingly, in a preferred aspect, the core element may further include

0 to approximately 20% by weight, preferably 5 to 10% by weight, based on the total weight of the core element of a plasticiser selected from the group consisting of diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, glycerol or mixtures thereof; optionally

0 to approximately 50% by weight, preferably 5 to 30% by weight, based on the total weight of the core element of a filler selected from the group consisting of

insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose and mixtures thereof; and optionally

0 to approximately 50% by weight, preferably 5 to 10% by weight, of a water-insoluble polymer selected from any suitable pharmaceutically acceptable polymer substantially insoluble independent of pH. The polymer may be selected from the group consisting of ethylcellulose, acrylic and/or methacrylic ester polymers or mixtures thereof and the like may be used. Polymers or copolymers of acrylates or methacrylates having a low quaternary ammonium content may be used. The acrylic acid ethyl ester: methacrylic acid ester (1:1) copolymer has been found to be suitable.

In a still further preferred aspect the core element may further include 0 to approximately 20% by weight, preferably 1 to 10% by weight of at least one surfactant selected from docusate sodium lecithin, polyoxethylene, sorbitan fatty acids (e.g. tweens) and sorbitan esters (e.g. spans). The surfactant sold under the trade designation Cremaphore RH410 has been found to be suitable.

In a preferred aspect of the present invention the core element of the pharmaceutical microparticle composition according to the present invention may include a core seed.

The size and amount of the core seed may vary substantially from approximately 100μm to 1700μm depending upon the amount of active ingredient to be included. Accordingly, the core seeds may vary from approximately 5 to 99% by weight, preferably 10 to 70% by weight based on the total weight of the core element, depending on the potency of the active ingredient. The core seed may be of such a diameter to provide a final core element having a diameter of approximately 200 to 2000μm.

The core seed may be of any suitable type. A sugar sphere or an active core seed may be used. The core element may further include other carriers or excipients,

stabilizing agents and colorants.

Where the matrix pharmaceutical microparticle composition includes an enteric coating on the core element, the enteric coating may be formed from an enteric polymer as described above. A hydroxypropyl methyl cellulose phthalate coating such as that sold under the trade designation HP50 or HP55 has been found to be suitable.

The enteric coating may further include a plasticiser.

Accordingly in a preferred aspect the enteric coating may include

approximately 40 to 100% by weight, preferably 70 to 95% by weight, based on the total weight of the enteric coating, of at least one enteric polymer,

0 to approximately 30% by weight, preferably 5 to 10% by weight, based on the total weight of the enteric coating of at least one plasticiser selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, dibutyl sebacate and glycerol.

The enteric coating may comprise from approximately 2 to 20% by weight, preferably approximately 4 to 10% by weight, of the pharmaceutical microcapsule composition.

In a preferred form the pharmaceutical microparticle composition may have the following formulation

Percentage ranges for the components of the pharmaceutical microparticle composition (percentages W/W):

	Preferred Range % w/w	More Preferred Range % w/w
Active Ingredient	(5-70)	(10-40)
Water Soluble Polymer	(10-80)	(15-60)
Core Seed	(10-80)	(15-60)
Enteric Polymer	(0.1-50)	(0.5-20)
Plasticiser	(0-10)	(0-1)

The core element may comprise a single or a

plurality of core layers.

In a preferred aspect of the invention, the core element comprises a single layer.

Accordingly in the preferred aspect of the invention there is provided a sustained release matrix pharmaceutical microparticle composition including

a core element comprising a single layer including

approximately 1 to approximately 95% by weight based on the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight of a polymeric component in a matrix therewith including

at least one water-soluble polymer; and

at least one enteric polymer;

and optionally

an enteric coating over the core element.

In a further preferred form the pharmaceutical microparticle composition may have the following formulation:

Percentage ranges for the components of the pharmaceutical microparticle composition (percentages W/W):

	Preferred Range % w/w	More Preferred Range % w/w
Nifedipine	(5-70)	(10-40)
PEG 6000	(10-80)	(15-60)
Sugar spheres	(10-80)	(15-60)
HP 50	(0.1-50)	(0.5-20)
Diethylphthalate	(0-10)	(0-1)

In an alternative preferred aspect of the invention, the core element comprises a plurality of core layers.

Accordingly in an alternative preferred aspect of the invention there is provided a sustained release pharmaceutical microparticle composition including

a core element including a plurality of core layers, wherein the core element includes

approximately 1 to approximately 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solublity; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

Preferably where the core element comprises a plurality of core layers, the outer core layer of the core element comprises the two polymers in matrix therewith.

The pharmaceutically active ingredient may be present in the outer core layer in any suitable effective amount. The amount of active ingredient is dependent on the potency of the active ingredient and on the desired dosage strength and volume of a unit dose of the drug product. The active ingredient may be present in amounts of approximately 0.1 to 95% by weight, based on the total weight of the outer core layer. The active ingredient may preferably be a dihydropyridine compound. The compound may be present in amounts of approximately 5 to 70% by weight, preferably 10 to 60% by weight, based on the total weight of the outer core layer.

The water-soluble polymer may be selected from the list of polymers as previously described. The polyethylene glycol sold under the trade designation PEG 6000 has been found to be suitable.

The water-soluble polymer may be present in the outer core layer in amounts of from approximately 10 to 80%, preferably 15 to 60% by weight, more preferably 30 to 50% by weight, based on the total weight of the outer core layer.

The enteric polymer may be selected from the list of polymers previously described. The hydroxypropyl methyl cellulose phthalates sold under the trade designation HP50 or HP55 have been found to be suitable.

The enteric polymer may be present in the outer core layer in an amount of up to approximately 50% by weight, preferably 1 to 20% by weight, more preferably 2 to 15% by weight, based on the total weight of the outer core layer.

Accordingly, in a preferred aspect of the present invention there is provided a sustained release matrix pharmaceutical microparticle composition including a core element including

approximately 1 to 95% by weight based on the total weight of the core element of a dihydropyridine compound;

a core seed;

approximately 20 to 90% by weight based on the total weight of the inner core layer of a water-soluble polymer in a matrix therewith; and

approximately 30 to 80% by weight based on the total weight of the outer core layer, of a water-soluble polymer; and

approximately 2 to 20% by weight based on the total weight of the outer core layer, of an enteric polymer in a matrix therewith,

and optionally an enteric coating over the core element.

As described above the pharmaceutical microparticle composition may include a plurality of core layers. The composition of the core layers may differ in the concentration or nature of the active ingredients therein. For example use of active ingredients of differing crystal size in adjacent layers is preferred. This may extend the period of sustained release even further.

The inner layer and outer core layer of the core element may be present in any suitable amounts in the pharmaceutical microparticle composition. The inner core layer (including sugar seeds where present) may comprise from approximately 40 to 95% by weight, preferably 50 to

85% by weight, of the pharmaceutical microparticle composition. The outer core layer may comprise from approximately 5 to 60% by weight, preferably 15 to 50% by weight, of the pharmaceutical microparticle composition.

Accordingly, the pharmaceutical matrix microcapsule composition may have the following formula:

	CORE ELEMENT			CORE COATING	
	Core Seed	Inner Core Layer	Outer Core Layer	Enteric Layer	Final Comp. %
Nifedipine		50 g	50 g		20.5
PEG 6000		100 g	50 g		30.7
Sugar spheres	200 g				40.6
HP50 (Hydroxypropyl-methylcellulose-phthalate)			10 g	32 g	8.5
Diethyl phthalate				3.5 g	0.6

The components of the core element other than the core seed, when present, may be provided in the form of a solution, dispersion or suspension.

In the form of a solution, the solvent or solvents may be present in amounts of from approximately 25 to 97% by weight, preferably 85 to 97% by weight, based on the total weight of the core formulation. The solvent for the core formulation may be a solvent such as methanol, ethanol, methylene chloride, acetone, isopropanol and mixtures thereof. Methanol, methylene chloride or a mixture thereof is preferred.

In a further aspect of the present invention, there is provided a method for preparing a sustained release pharmaceutical microparticle composition providing

a core seed;

a core formulation including

an active ingredient of very low solubility;

at least two polymers capable of forming a

matrix with the active ingredient; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the core formulation onto the core seed to form a matrix core element; and

drying the core element.

The core seed may include a sugar sphere. The active ingredient may be a dihydropyridine compound, preferably nifedipine.

Where a plurality of core layers are to be used the method may further include

providing

a core layer formulation including

at least one active ingredient of very low solubility;

at least two polymers including a water-soluble polymer; and optionally

an enteric polymer; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying successive layers onto the core seed to form the matrix core element wherein at least one layer includes the core layer formulation.

Where an enteric coating is to be used, the method may further include

providing

a sustained release pharmaceutical microparticle; and

an enteric coating formulation including

an enteric polymer; optionally

a plasticiser; and

a solvent therefor

introducing the microparticle into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the enteric coating formulation onto the microparticle to form a sustained release microcapsule.

The sustained release core element and sustained

release microcapsules may be subjected to a drying step. The drying step may be conducted in a fluidised bed or drying oven.

Spray coating of core elements may be undertaken utilizing bottom or Wurster, top or tangentially located spray nozzles. A bottom spray nozzle may reside proximate to the base of the fluidised bed facing upwards while a top spraying nozzle is located above the contents of the bed and facing downwards. The spray nozzle may reside in the mid-section of the fluidised bed and be oriented such as to spray tangentially to the rotating core elements.

The sustained release matrix pharmaceutical microparticle composition according to the present invention may include a plurality of microparticles.

The sustained release pharmaceutical composition may be provided in any suitable unit dosage form. An encapsulated form may be used. The pharmaceutical microparticle composition may be provided in a pellet or tabletted pellet form. A tablet may be formed by compression of the pellets optionally with the addition of suitable excipients.

The sustained release pharmaceutical microparticle composition may be in multi-pellet encapsulated, sprinkle, sachet or tabletted forms.

The sustained release pharmaceutical microparticle composition may be administered under a similar dosage regimen to that used in the prior art. However, it is preferred that the pellet composition be administered less frequently. The multi-pellet encapsulated form may for example be administered once every 12 hours, preferably once every 24 hours.

In a preferred aspect of the present invention the sustained release pharmaceutical pellet composition incorporating the dihydropyridine compound may provide effective vasodilation with once daily administration. Versatility of dosing may be achieved with 20 to 90 mg or any other dose strength of capsules required.

In accordance with a further aspect of the present invention, there is provided a method of treating

cardiovascular related conditions in patients requiring such treatment which method includes administering to a patient an effective amount of a sustained release pharmaceutical microparticle composition including

a core element including a dihydropyridine; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

The method of treatment according to this aspect of the present invention is particularly applicable to the treatment of Hypertension and/or Angina pectoris due to coronary heart disease, particularly Angina pectoris related to coronary artery spasm, utilising for example nifedipine.

Preferably the sustained release pharmaceutical microparticle composition is provided in a unit dosage form and administration occurs at intervals of approximately 12 to 24 hours.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

EXAMPLES

A. SINGLE LAYERED OR "ONE STEP" CORES

EXAMPLE 1 (1/1.5/0.1)*

Formulation		(g)
Sugar spheres	30/35 mesh	200
Nifedipine		100
PEG 6000		150
HP 50		10
Methanol **		540
Methylene Chloride **		540

Finished cores are between 710 - 1000 µm with potency of 22%, yield 460 g.

EXAMPLE 2 (1/1.5/0.3)*

Formulation		(g)
Sugar spheres	30/35 mesh	600
Nifedipine		143
PEG 6000		214.5
HP 50		42.9
Methanol **		1158.3
Methylene Chloride **		1158.3

Finished cores are between 600 - 850 µm with potency of 14%, yield 1000 g.

EXAMPLE 3 (1/1.3/0.2)*

Formulation		(g)
Sugar spheres	30/35 mesh	600
Nifedipine		133.3
PEG 6000		173.3
HP 50		26.7
Methanol **		900
Methylene Chloride **		900

Finished cores are between 600 - 850 µm with potency of 14%, yield 933 g.

Examples 1 to 3 illustrate how the ratio of polymers may be varied to the desired release profile.

EXAMPLE 4 (1/1/0.2)*

Formulation		(g)
Sugar spheres	30/35 mesh	200
Nifedipine		100
PEG 6000		100
PVAP		20
Methanol **		500
Methylene Chloride **		500

Finished cores are between 600 - 850 µm with potency of 24%, yield 420 g.

Example 4 uses a different enteric polymer to Examples 1 to 3.

EXAMPLE 5 (1/1/0.2)*

Formulation		(g)
Sugar spheres	35/45 mesh	600
Nifedipine		208
PEG 6000		208
HP 50		41.6
Methanol **		1123
Methylene Chloride **		1123

Finished cores are between 500 - 710 µm with potency of 19%, yield 1057 g.

Notes: * Defines Nifedipine/Water Soluble Polymer/Enteric Polymer Ratio

** Not present in final formulation.

PROCESS FOR EXAMPLES 1 TO 4 (CORE MANUFACTURE)

To a Fuji Paudal Q400 spheroniser for Examples 1 and 4 or Glatt WSG1 for Examples 2, 3 and 5 the sugar spheres are charged. A dissolved solution containing nifedipine PEG 6000 and HP50 (or PVAP, for Example 4) in a mixture of methanol/methylene chloride (50/50) was applied as atomised droplets onto the sugar spheres. The finished cores are dried for 15 minutes at 40°C.

B. DOUBLE LAYERED or "TWO STEP" SUSTAINED RELEASE CORE

EXAMPLE 6

	CORE ELEMENT		
	Sugar Seed	Inner Core Layer	Outer Core Layer
Nifedipine		50g	50g
PEG 6000		100g	50g
Sugar spheres 30/35	200g		
HP50			10 g
Methylene Chloride**		250	300
Methanol**		250	300

Finished cores are between 710 - 1000 µm with potency of 22% and yield of 460 g.

EXAMPLE 7

	CORE ELEMENT		
	Sugar Seed	Inner Core Layer	Outer Core Layer
Nifedipine		200g	125g
PEG 6000		400g	125g
Sugar Spheres 35/45	300g	-	-
HP 50		-	25g
Methanol **		1000g	675g
Methylene Chloride **		1000g	675g

Finished cores are between 600-850µm with potency of 28% and yield of 1075g.

PROCESS FOR EXAMPLE 6 AND 7 (CORE MANUFACTURE)

To a Fuji Paudal Q400 spheroniser the sugar spheres are charged. A dissolved solution containing the nifedipine, PEG 6000 and mixture of methanol/methylene chloride (50/50) was applied as atomised droplets onto the sugar spheres. The finished inner cores are dried at 40°C for 15 minutes. This batch is returned to commence the second stage or second layer. To this charge a dissolved

solution containing the nifedipine, PEG 6000 and HP50 in the methanol/methylene chloride mixture was supplied as atomised droplets onto the inner cores. The finished cores are dried at 40°C for 15 minutes.

ENTERIC COATING OF CORES

The cores produced from Example 6 was enteric coated using the following process.

To the Glatt WSG/1, 1.6 kg of cores were charged. A dissolved solution containing 117.6 g HP50, 13g of diethyl phthalate in 1.96 kg of ethanol/water mixture was applied as atomised droplets to the fluidising cores. On completion of the spray, the pellets were dried for 50 minutes at an inlet air temperature of 41°C. The weight gain was recorded as 5.8% w/w.

IN-VITRO TESTING

In vitro dissolution profiles were generated at pH 6.8 for Examples 1 to 7 above utilising the following test method dissolution.

Each formulation included 60 mg equivalent to nifedipine and was dissolved in 900 mL at pH of 6.8 with surfactant and an orthophosphate buffer. The apparatus used is baskets. Sampling is carried out using a 0.45 μm filter and samples were determined using a UV spectrophotometer at a wavelength of 340 nm.

The results are provided in Figures 1 to 7.

IN VIVO TESTING

Mean nifedipine concentrations were generated in vivo utilising Example 6 above. These were compared with comparison formulations A and B (see below).

A three way single dose cross over pilot study was performed to assess the bioequivalence of the nifedipine formulations, including batches of Example 6, comparison A and comparison B (reference). Eighteen healthy male subjects received a single 60 mg dose of a formulation after an overnight fast. At the end of the study, each subject had received two formulations (out of a possible 4) and the reference formulation (B). Plasma samples from all subjects were analysed for nifedipine using a validated chromatographic procedure.

Comparison A is not in accordance with the invention and comprises an uncoated core where micronised nifedipine is layered onto sugar spheres.

The formulation comprises

COMPARISON A	W/W%
Nifedipine	31.85
Hydroxypropyl Cellulose	4.14
Polyoxyethylene 20 sorbitan	0.32
Sugar spheres 20/25 mesh	63.69

It does not contain a matrix composition, and as can be evidenced by the high initial plasma peak, does not produce a suitable sustained release profile.

Comparison B is the existing commercially available sustained release product Procardia XL, 60 mg extended release tablets by Pfizer.

The results are provided in Figure 8.

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

Claims

1. A sustained release pharmaceutical microparticle composition including

a core element including

an active ingredient of very low solubility; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

2. A microparticle composition according to claim 1, wherein the polymer components include

a polymer which is at least partially water-soluble (water-soluble polymer); and

a polymer which is substantially insoluble at acidic pH but at least partially soluble at a less acidic to basic pH (enteric polymer).

3. A microparticle composition according to claim 2, wherein

the water-soluble polymer is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof; and

the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof.

4. A microparticle composition according to claim 3, wherein

the water-soluble polymer is present in an amount of from approximately 10 to 80% by weight, based on the total weight of the core element; and

the enteric polymer is present in amounts from 0.1% to approximately 50% by weight, based on the total weight of the core element.

5. A microparticle composition according to claim 1 wherein the active ingredient includes a dihydropyridine.

6. A microparticle composition according to claim 5

wherein the dihydropyridine is nifedipine.

7. A microparticle composition according to claim 1, further including

0 to approximately 50% by weight, based on the total weight of the core element of a plasticiser selected from the group consisting of diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, glycerol, dibutyl sebacate or mixtures thereof; optionally

0 to approximately 50% by weight, based on the total weight of the core element of a filler selected from the group consisting of insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose and mixtures thereof; and optionally

0 to approximately 50% by weight, of a water-insoluble polymer selected from the group consisting of ethyl cellulose, acrylic and/or methacrylic ester polymers or mixtures thereof.

8. A microparticle composition according to claim 7 further including approximately 1 to 10% by weight based on the total weight of the core element, of a surfactant.

9. A microparticle composition according to claim 1, wherein the core element includes a core seed.

10. A sustained release pharmaceutical microparticle composition including

a core element including

approximately 1 to approximately 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight of a polymeric component in a matrix therewith including

a water-soluble polymer; and

an enteric polymer;

and optionally

an enteric coating over the core element.

11. A sustained release pharmaceutical microparticle composition including

a core element including a plurality of core layers, wherein the core element includes

approximately 1 to approximate 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

12. A sustained release matrix pharmaceutical microparticle composition including a core element including

approximately 1 to 95% by weight based on the total weight of the core element of a dihydropyridine compound;

a core seed;

approximately 20 to 90% by weight based on the total weight of the inner core layer of a water-soluble polymer in a matrix therewith; and

approximately 30 to 80% by weight based on the total weight of the outer core layer, of a water-soluble polymer; and

approximately 2 to 20% by weight based on the total weight of the outer core layer, of an enteric polymer in a matrix therewith,

and optionally an enteric coating over the core element.

13. A microcapsule composition including a microparticle composition according to claim 1, further including approximately 2 to 20% by weight of an enteric coating over the core element.

14. A microcapsule composition according to claim 13,

wherein the enteric coating includes

approximately 40 to 100% by weight, based on the total weight of the enteric coating, of at least one enteric polymer,

0 to approximately 30% by weight, based on the total weight of the enteric coating of at least one plasticiser selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, dibutyl sebacate and glycerol.

15. A method for preparing a sustained release pharmaceutical microparticle composition providing

a core seed;

a core formulation including

an active ingredient of very low solubility;

at least two polymers capable of forming a matrix with the active ingredient; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the core formulation onto the core seed to form a matrix core element; and

drying the core element.

16. A method according to claim 15, further including providing

a core layer formulation including

an active ingredient of very low solubility;

at least two polymers including a water-soluble polymer; and optionally

an enteric polymer; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying successive layers onto the core seed to form the matrix core element wherein at least one layer includes the core formulation.

17. A method according to claim 16 wherein the core element includes

approximately 1 to approximate 95% by weight

based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

18. A method according to claim 15, further including providing

a sustained release pharmaceutical microparticle; and

an enteric coating formulation including

an enteric polymer; optionally

a plasticiser; and

a solvent therefor

introducing the microparticle into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the enteric coating formulation onto the microparticle and then spraying an enteric coating formulation onto the core element to form a sustained release coated pellet.

19. A method according to claim 15 wherein

the water-soluble polymer is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof; and

the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof.

20. A method according to claim 19 wherein

the water-soluble polymer is present in an amount

of from approximately 10 to 80% by weight, based on the total weight of the core element; and

the enteric polymer is present in amounts from 0.1% to approximately 50% by weight, based on the total weight of the core element.

21. A method according to claim 20 wherein the active ingredient includes a dihydropyridine.

22. A method according to claim 21 wherein the dihydropyridine is nifedipine.

23. A method of treating cardiovascular related conditions in patients requiring such treatment which method includes administering to a patient an effective amount of a sustained release pharmaceutical microparticle composition including

a core element including a dihydropyridine; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

24. A method according to claim 23 wherein the microparticle composition is administered at intervals of approximately 24 hours or more.

25. A method according to claim 23 wherein the dihydropyridine is nifedipine.

26. A method according to claim 23 wherein

the water-soluble polymer is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof; and

the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof.

27. A method according to claim 23 wherein

the water-soluble polymer is present in an amount of from approximately 10 to 80% by weight, based on the total weight of the core element; and

the enteric polymer is present in amounts from

0.1% to approximately 50% by weight, based on the total weight of the core element.

28. A method according to claim 23 wherein the microparticle composition includes

a core element including a plurality of core layers, wherein the core element includes

approximately 1 to approximate 95% by weight based on the total weight of the core element of a dihydropyridine; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

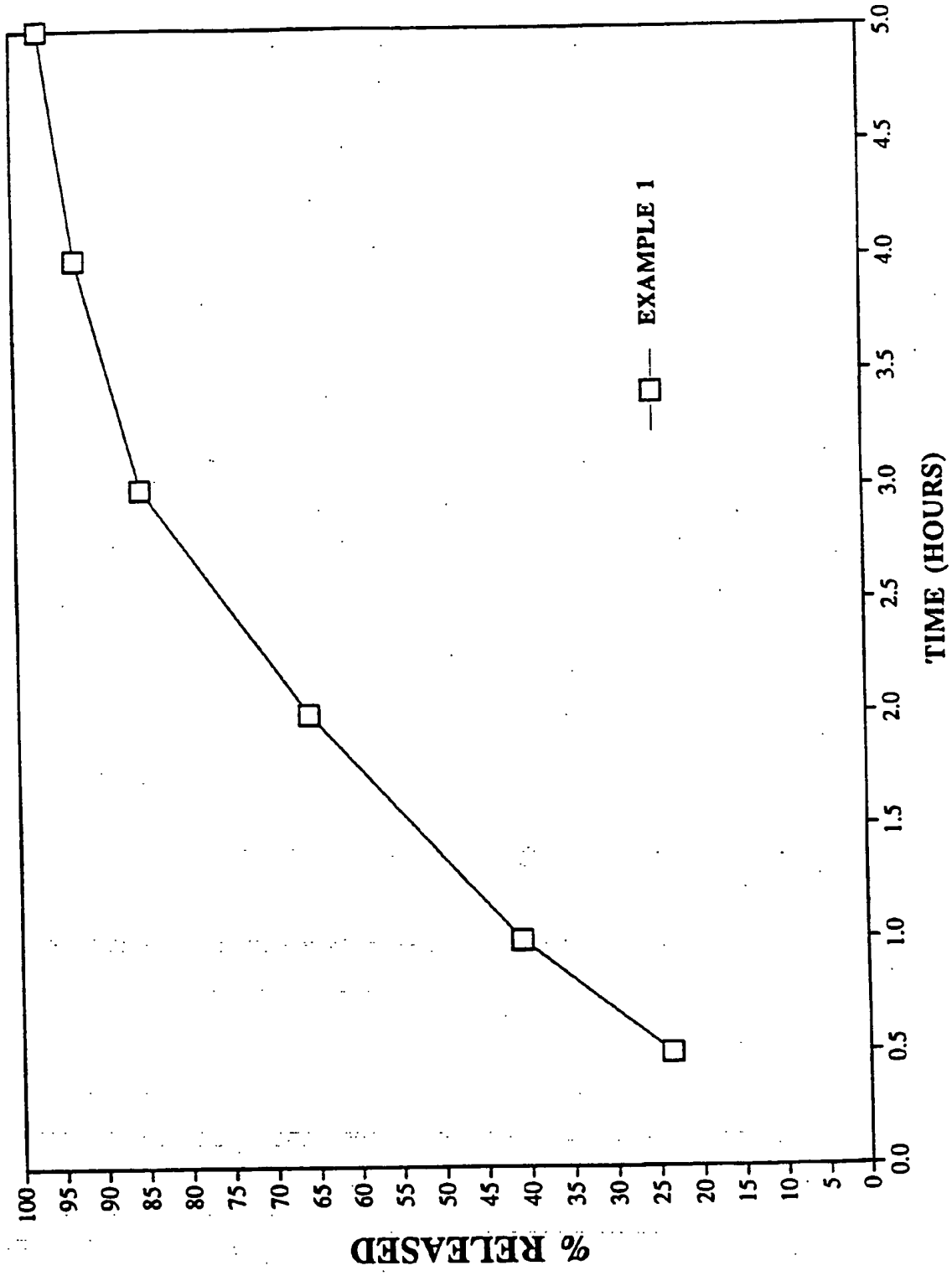
29. A method according to claim 28 wherein the dihydropyridine is nifedipine.

30. A microparticle composition according to claim 1, wherein the composition is in a unit dosage form.

31. A microparticle composition according to claim 30 wherein the composition is in a pellet or tabletted pellet form.

32. A microparticle composition according to claim 1 wherein the active ingredient is in a crystalline form.

Figure 1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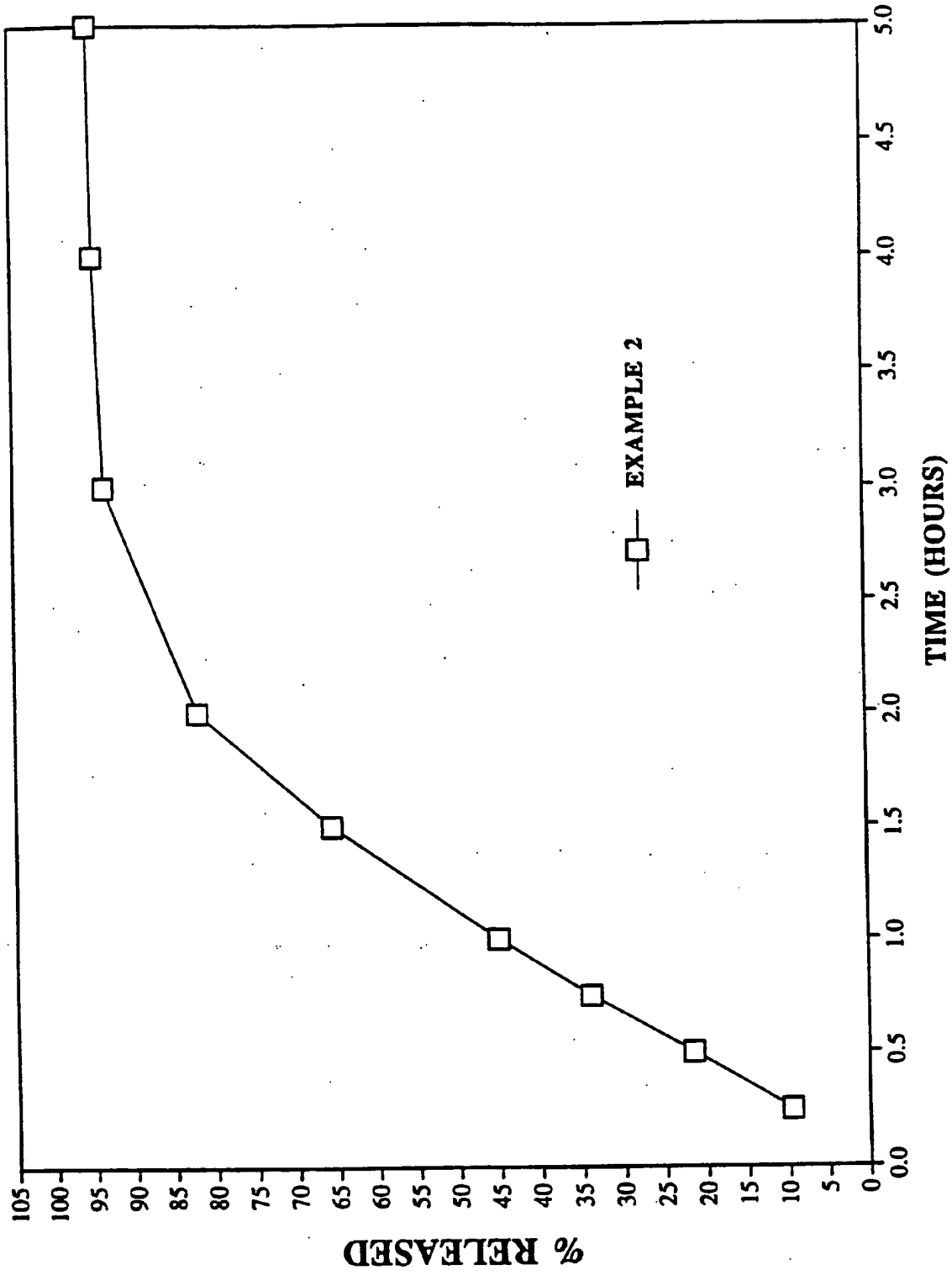
TIME (HOURS)
EXAMPLE 1

Figure 2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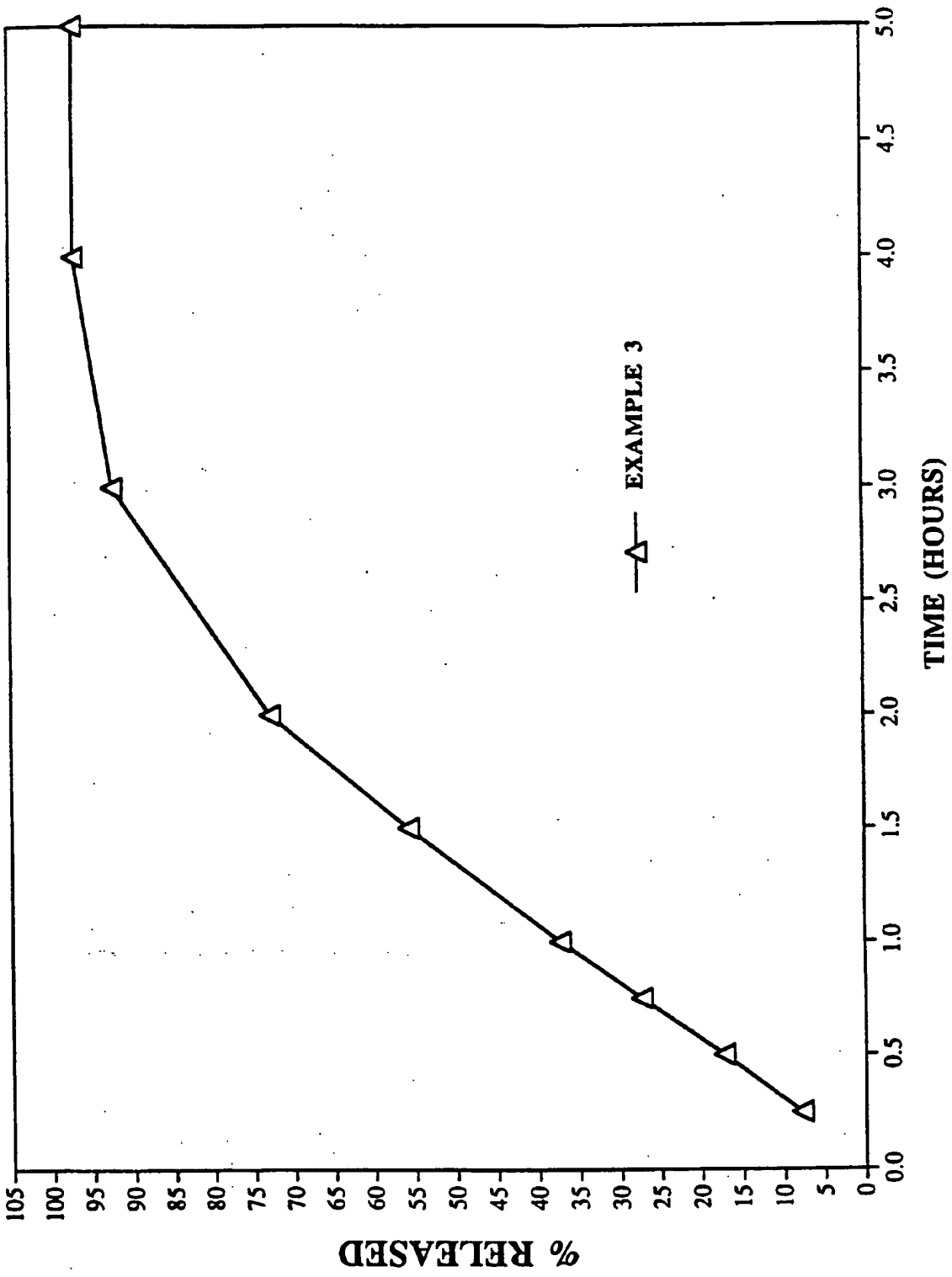
TIME (HOURS)
EXAMPLE 2

Figure 3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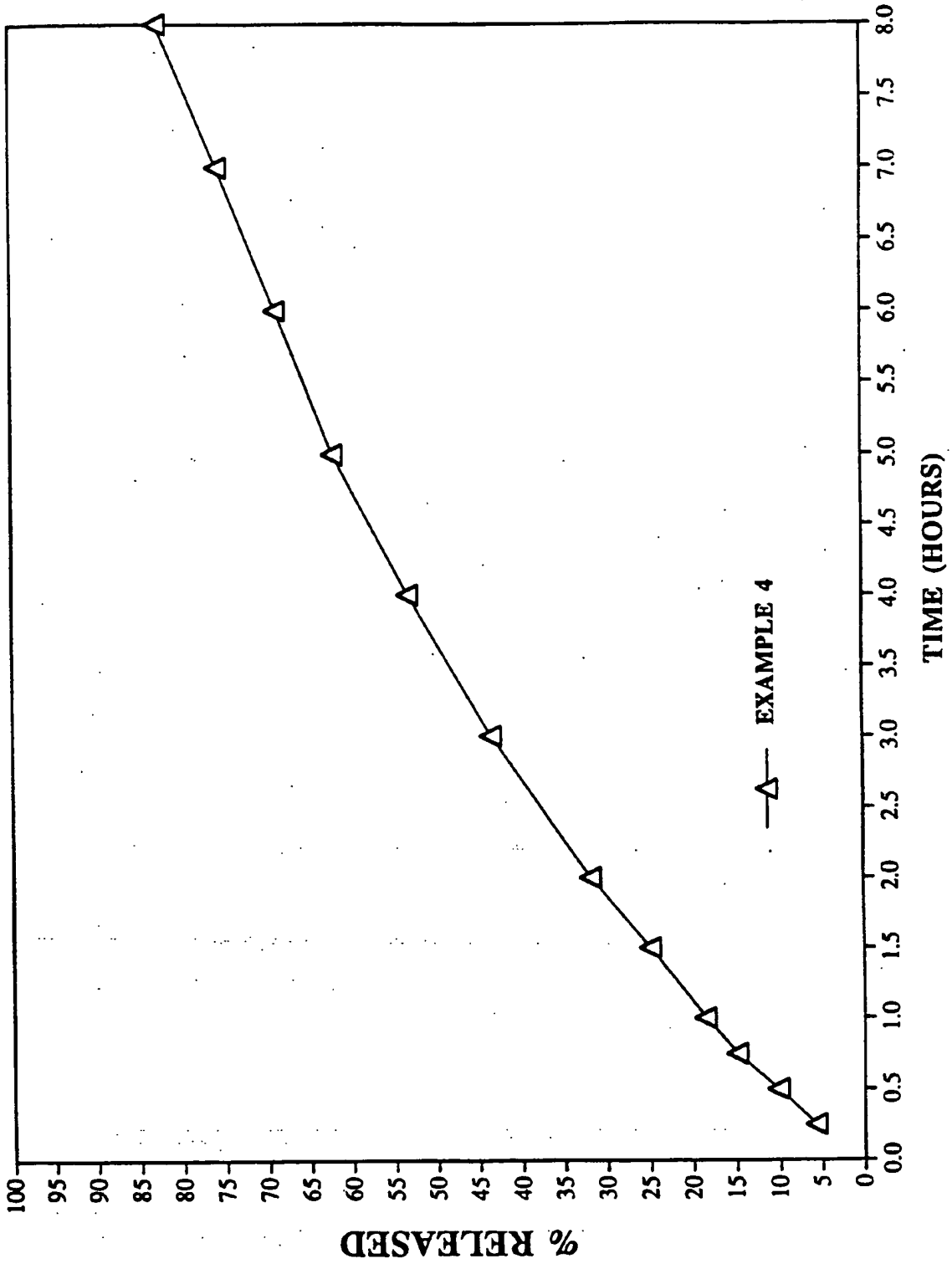
TIME (HOURS)
EXAMPLE 3

Figure 4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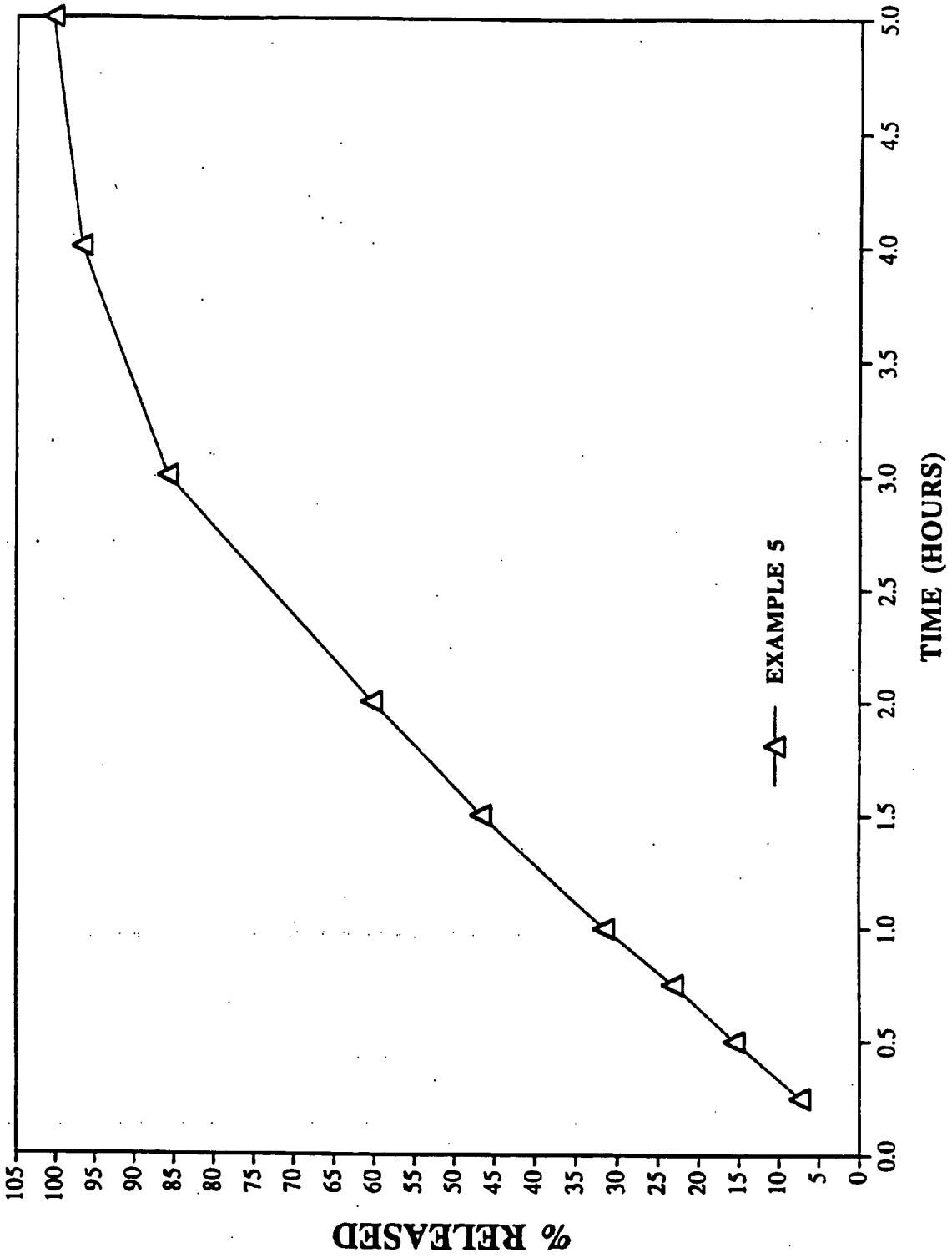
TIME (HOURS)
EXAMPLE 4

Figure 5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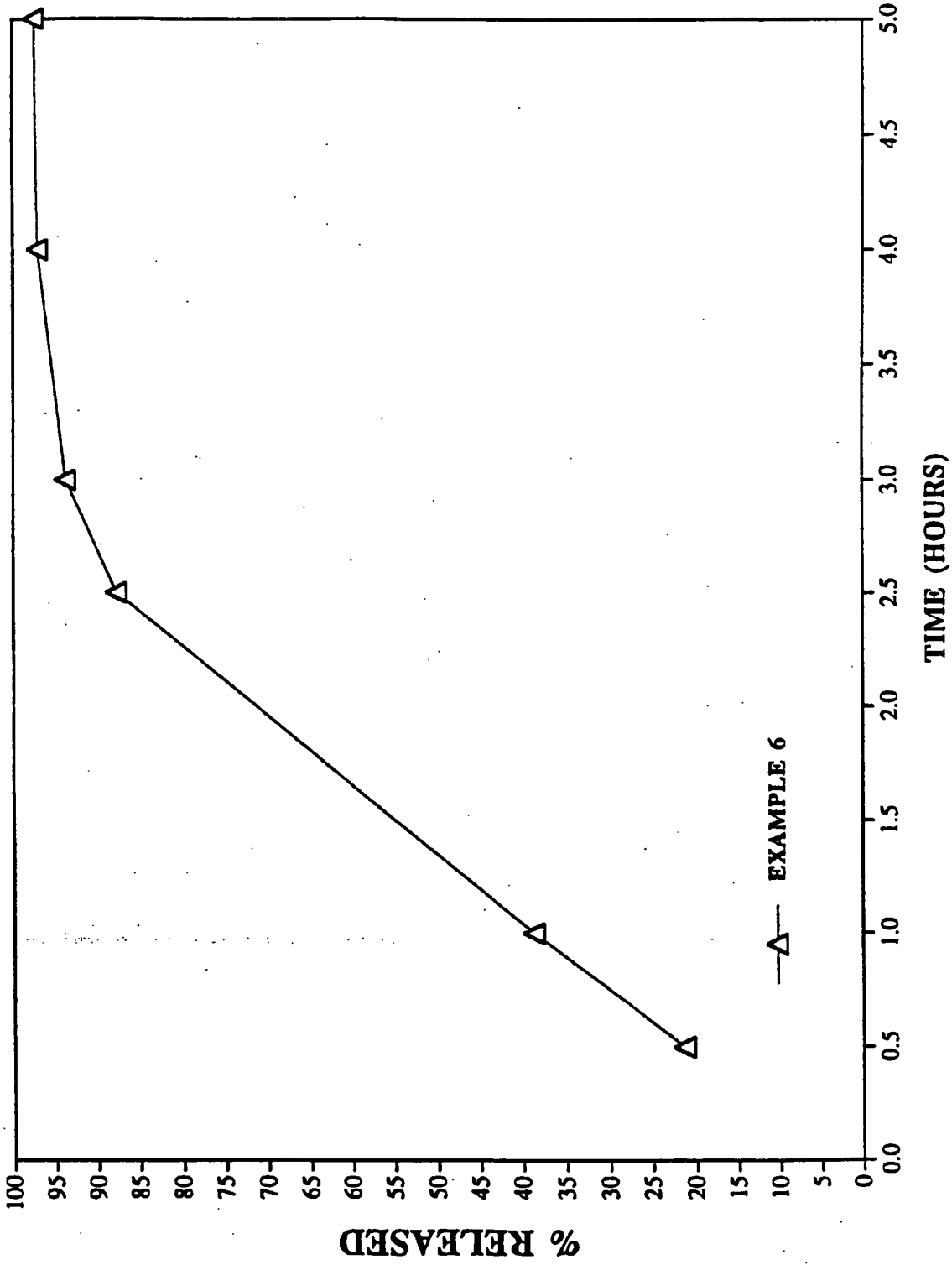
TIME (HOURS)
EXAMPLE 5

Figure 6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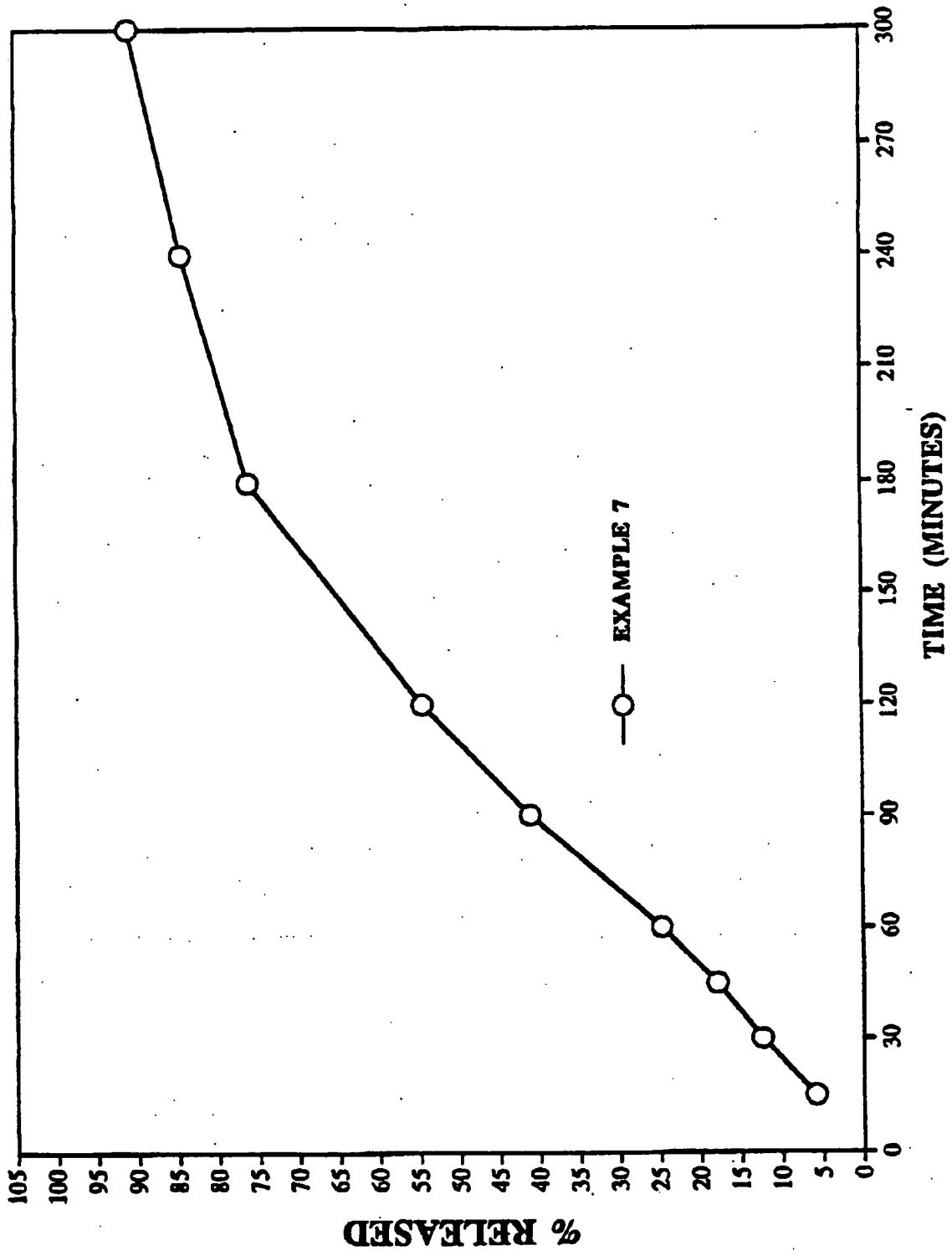
TIME (HOURS)
EXAMPLE 6

FIGURE 7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EXAMPLE 7
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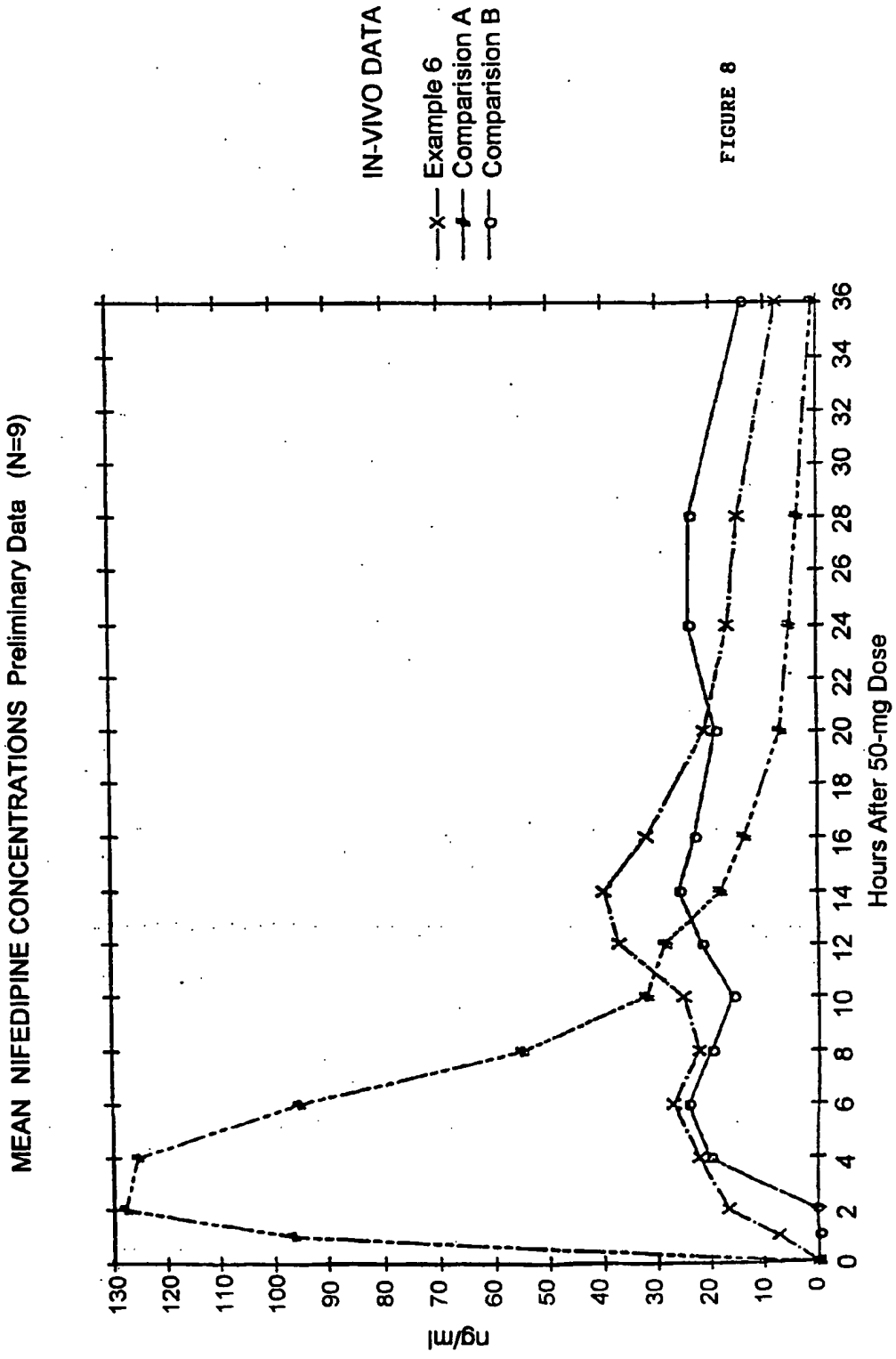

FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00462

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.[5] A61K 9/16, 9/52, 9/22, 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 9/16, 9/52, 9/26, 9/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT: low()solubil: and polymer:; nifedipine# and polymer#
JAPIO: low()solubil: and polymer:; nifedipine# and polymer#

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	AU,B,49594/85 (588258) (PHARMATEC S.P.A.) 8 April 1986 (08.04.86) See entire document	1-6, 9, 10, 15, 20-23, 25-27, 30-32
X	WO,A,89/02738 (APS RESEARCH LTD.) 6 April 1989 (06.04.89) See entire document	1, 2, 5, 6, 10, 13, 23, 25, 27, 30, 31
P, X	WO,A,93/13773 (ETHICAL PHARMACEUTICALS LTD.) 22 July 1993 (22.07.93) See entire document	1, 2, 5, 6, 9, 10, 15, 23, 25, 27, 30, 31

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 DECEMBER 1993 (23.12.93)	24 DEC 1993 (24.12.93)

Name and mailing address of the ISA/AU

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00462

Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X	EP,A,387782 (EGIS GYOYSZERGYAR) 19 September 1990 (19.09.90) See entire document	1-6, 10, 23, 25-27, 30-31
X	AU,B,68207/87 (592618) (ELAN CORPORATION P.L.C.) 14 July 1988 (14.07.88) See entire document	1-6, 10, 30-32
X	Patent Abstracts of Japan C-877, page 4, JP,A,3-169814 (NIPPON YAKUHIN KOGYO K.K.) 23 July 1991 (23.07.91) Abstract	1, 2, 4, 5, 10, 23, 25, 29, 31
X	Patent Abstracts of Japan, C-353, page 35, JP,A,61-17510 (TOYO BOSEKI K.K.) 25 January 1986 (25.01.86) Abstract	1, 2, 5, 6, 10, 23, 25, 30
X	US,A,4740365 (TOYO BOSEKI KABUSHIKI KAISHA) 26 April 1988 (26.04.88) See entire document	1, 2, 5, 6, 10, 11, 30, 31
X	EP,A,220760 (EURAND ITALIA S.P.A.) 6 May 1987 (06.05.87) See entire document	1, 5, 6, 30, 31, 32
X	GB,A,1579818 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 26 November 1980 (26.11.80) See entire document	1, 5, 6, 23, 30, 31
X	AU,B,58284/86 (595801) (EUROCELTIQUE S.A.) 18 December 1986 (18.12.86) See entire document	1, 5, 6, 30, 31
X	Patent Abstracts of Japan, C-438, page 37, JP,A,62-48618 (ZERIA SHINYAKU KOGYO K.K.) 3 March 1987 (03.03.87) Abstract	1-3, 5-6, 30-31
x	DD,A,295550 (MARTIN-LUTHER UNIVERSITAT) 7 November 1991 (07.11.91) See entire document	1, 5, 6, 23, 25, 30-31

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member					
AU	49594/85	CA	1253079	DE	3582251	DK	2221/86
		EP	226588	ES	547707	FI	871116
		IT	1178511	JP	4017932	NO	171887
		PT	81113	WO	8601717	YU	1439/85
		ZA	8506862				
AU	58284/86	CA	1277913	DK	2730/86	EP	205282
		ES	555899	FI	862479	JP	61286321
		KR	8902949	NO	172027	PT	82746
		US	4940587	ZA	8604105		
AU	68207/87	CA	1288049	CS	9104177	DE	3779414
		DK	528/87	EP	274176	JP	63174929
		NZ	219140				
US	4740365	DE	3580384	EP	159604	JP	60215622
WO	8902738	EP	386023				
WO	93/13773	AU	32636/93				
EP	220760	AU	63832/86	CA	1280976	DE	3680989
		DK	4811/86	FI	87424	JP	62167727
		NO	172168	NZ	217841	US	4880623
		ZA	8607767				
GB	1579818	DE	2822882	JP	54002316	US	4412986
EP	387782	CA	2012194	CH	680416	EP	387782
		FR	2644343	GB	2229095	JP	2279626
		US	5108757	YU	458/90		

END OF ANNEX